REMARKS

Reconsideration of the above-identified patent application in view of the amendment above and the remarks below is respectfully requested.

No claims have been canceled in this paper. Claims 1-7, 9 and 10 have been amended in this paper. New claims 12-14 have been added in this paper. Therefore, claims 1-14 are pending and are under active consideration.

Claims 1-11 stand rejected under 35 U.S.C. 112, first paragraph, "because the specification, while being enabling for recognizing and diagnosing acute myocardial infarction, does not reasonably provide enablement for all acute coronary syndromes." In support of the rejection, the Patent Office states the following:

> The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claims.
>
> Upon inspection of the instant specification, it appears that all correlations are directed towards CCTD and myocardial infarction. While applicant does point out that levels of CCTD below the limit may be indicative of other coronary troubles, such a correlation does not appear to be absolute, as is the case with myocardial infarctions. In fact, it appears that more of a correlation is made between such coronary troubles as angina pectoris and troponin levels. At best, on page 22, the specification does seem to support instable angina pectoris along with myocardial infarction which may be diagnosed on choline measurements. The instant claims, however, are directed to CCTD measurement and content and do not consider troponin levels. Thus, the instant claims do not seem to be commensurate in scope with instant disclosure. Further clarification and/or correction is required.

Applicants respectfully traverse the foregoing rejection. As best understood by Applicants, the Patent Office is apparently taking the position that, although the present specification is enabling

for certain acute coronary syndromes, such as acute myocardial infarctions, the specification is not enabling for other acute coronary syndromes, such as unstable angina pectoris. It further appears to Applicants that the Patent Office's position is predicated on the contention that the specification does not conclusively establish that CCTD levels can be used to make a diagnosis of an unstable angina pectoris.

In response, Applicants note that it is not Applicants' responsibility to prove enablement. Instead, the specification is presumed to be enabling, and it is the Patent Office's burden to prove non-enablement. To prove non-enablement, the Patent Office must provide a reasoned basis for a person of ordinary skill in the art who has read the specification to question the enablement of the specification. Given that the Patent Office's position of non-enablement appears to be predicated on an alleged lack of operability of the invention for acute coronary syndromes other than myocardial infarctions, it is the burden of the Patent Office to prove that a person of ordinary skill in the art who has read the specification would question the operability of the invention for acute coronary syndromes other than myocardial infarctions. Applicants respectfully submit that the Patent Office has failed to meet its burden.

In any event, it should be noted that unstable angina pectoris frequently is a precursor to acute myocardial infarction, such that methods that have proven to be useful in the diagnosis of acute myocardial infarction are also useful when diagnosing unstable angina pectoris and should, therefore, be used accordingly.

The close correlation between unstable angina pectoris and acute myocardial infarction had been generally acknowledged at the time of filing of the application. For example, in August 1998, S.L. Chiercha stated at the Congress of the European Society of Cardiology:

> "Unstable angina is heterogeneous condition which marks the transition from stable coronary artery disease to a state in which the patient is at high risk of progressing to myocardial infarction (MI) or death" (S.L. Chierca, Current therapeutic strategies in unstable angina, European Heart Journal, 1999; 1(Suppl N): N2-N6).

The fact that unstable angina pectoris can transgress to an acute myocardial infarction is also reflected in other terms used for unstable angina, such as "impending myocardial infarction" or "preinfarction angina." For example, van Miltenburg-van Zil wrote in 1995:

> "The clinical syndrome" unstable angina "encompasses a variety of clinical presentations of transient episodes of myocardial ischemia...Other terms have been used to describe the syndrome, such as impending myocardial infarction, perinfarction angina, acute coronary insufficiency..." (Van Miltenburg-van Zil et al, Incidence and follow-up of Braunwald subgrounds in unstable angina pectoris, J. Am. Coll. Cardiol., 1995, 25:1286-92)

Furthermore, it was also generally acknowledged at the time of the filing of the patent application that unstable angina pectoris and acute myocardial infarction exhibit a common pathogenesis in essential parts. For example, S.L. Chiercha stated in August 1998 at the Congress of the European Society of Cardiology:

> "Unstable angina and MI (myocardial infarction) share a common underlying pathogenesis: disruption of an atherosclerotic plaque followed by platelet aggregation and thrombus formation." (S.L. Chiercha, Current therapeutic strategies in unstable angina, European Heart Journal, 1999, 1(Suppl N):N2-N6).

The common pathogenesis of unstable angina and of acute myocardial infarction also implies that methods that have proven useful in the diagnosis of acute myocardial infarction are also useful with unstable angina pectoris.

The danger of a patient with unstable angina of developing an acute myocardial infarction is one of the fundamental foundations of the Braunwald-classification which is also mentioned in

the present specification on page 1. (Braunwald et al., 1994, Diagnosing and managing unstable angina, Agency for Health Care Policy and Research, Circulation, 90:613-622). This reference discloses that the risks of unstable angina pectoris also form the basis for diagnostic and therapeutic strategies with respect to acute myocardial infarction. The Agency of Health Care Policy and Research Guidelines also state that the borders between unstable angina pectoris and acute myocardial infarction are very often ill defined:

> "As a clinical syndrome, unstable angina shares ill-defined borders with...acute MI (myocardial infarction), a presentation with higher risk."

Therefore, unstable angina pectoris and acute myocardial are very often grouped together and are termed together as acute coronary syndrome. This is also the case in the present application, which reads (page 1, second paragraph):

> "Acute coronary syndromes comprise the syndromes of acute myocardial infarction and unstable angina pectoris...."

The fact that patients having unstable angina pectoris and acute myocardial infarction represent a continuum, since both indications display a common pathophysiology of myocardial ischemia, is also disclosed in the present application on page 19/20:

> "As is well known, the prognosis of patients suffering from unstable angina pectoris is worse if increased values of cardial troponins are discovered in the progress thereof (Ohmann, E.M., 1996, N Engl J Med, 335:1333-41). It is assumed that these patients not only go through myocardial ischemia but also suffer myocardial micronecrosis...."

In this publication, Ohmann has clearly pointed out the close relationship between unstable angina pectoris and acute myocardial infarction on one side with the common pathophysiology of myocardial ischemia on the other side, which ischemia can then progress to myocardial necrosis:

> "Patients who come to the hospital with acute ischemic symptoms represent a continuum of disease from unstable angina to acute infarction."

This continuum or spectrum of unstable angina to the acute myocardial infarction is also pointed out in the publication of Ryan, T.J. et al., 1996, J am Coll Cardiol, 28:1328-1428, which is mentioned on page 22 of the present application. In this publication, on page 1342, the following statement is made:

> The spectrum of clinical conditions ranging from unstable angina to non-Q-wave-AMI (AMI=acute myocardial infarction) to Q-wave-AMI is referred to as acute coronary syndromes.

Contrary to the Patent Office's assertions, CCTDs are, in fact, markers for the entire group of acute coronary syndromes, in particular acute myocardial infarction and unstable angina, and this is disclosed in the present application at several places:

a) page 3-4: "Results obtained by the applicants show that the activation of various myocardial phospholipases in the early phase of the acute myocardial infarction as well as disturbances of the lipid metabolism upon severe myocardial ischemia bring about a distinct release of choline, choline derivatives, and of chemically related trimethyl ammonium derivatives, such as phosphoryl choline, plasmalogens, or lysoplasmenyl choline, thereby provoking an increase in concentration of CCTD in certain body fluids and component parts of the body."

b) page 4: "...their similar behavior in pathophysiological processes, i.e. the very early release from the heart by ischemic membrane destruction are the reason for looking at them together, as CCTD." Since "ischemic membrane destruction" represents a common pathophysiology of unstable angina pectoris and of the acute myocardial infarction, CCTD, in their diagnostic application, relate to the diagnosis of both indications.

c) page 7: "Certain activated phospholipases are significant in their cardial release of CCTD in the context of ischemic membrane destruction of cardial muscle cells." Since "ischemic membrane destruction" represents a common pathophysiology of both unstable angina pectoris and of acute myocardial infarction, CCTD, again, relates to the diagnosis of both indications.

d) page 17: "...The same applies to diagnosing unstable angina pectoris in which case the limit values must be set by examining a sufficiently great number of patients and in consideration of the diagnostic questions to be answered." In this passage, it is emphasized that, for the diagnosis of unstable angina, limit values are to be taken into account, depending on the method and the question to be answered. This passage, however, also clearly indicated that CCTD may be used also for the diagnosis of unstable angina pectoris.

e) page 20: The present application also discloses that CCTD may also be released in minor ischemic damages occur, i.e. during so called "minor myocardial damages" and "myocardial micronecrosis." In patients having an uncomplicated course of events there are no elevated levels of CCTD observed. For example, page 20 reads: "The examinations by the applicants have revealed that patients with angina pectoris and an uncomplicated course of the disease do not have elevated levels of CCTD, whereas the CCTD values are higher for all those patients with myocardial micronecroses." The conclusion drawn by the Patent Office from this passage that CCTD were not a useful marker for unstable angina pectoris is not appropriate. The quoted passage only implies that CCTD levels do not increase with patients having unstable angina pectoris and an uncomplicated course of events. On the contrary, patients having unstable angina pectoris and a complicated course of events are very well identified by CCTD as a marker. In fact, the passage just quoted actually shows the advantages associated with CCTD over troponins. This is because CCTD may be released

even with the smallest myocardial damages and with myocardial damages of short duration due to their small size, which damages may not coincide with elevated levels of troponins since troponins have a much higher molecular weight and are thus released only during larger and sufficiently long myocardial damages. This much higher sensitivity of CCTD also becomes evident from the fact that CCTD have already increased in 100% of all samples whereas troponin have only done so in 50% of all cases (page 19, first paragraph). Also the rapid onset of an elevation of CCTD within the first three hours after beginning of myocardial ischemia shows that CCTD is highly sensitive because of its early release during myocardial ischemia and therefore does not even require major myocardial necrosis or myocardial infarction to be present. Already one hour after the beginning of ischemia CCTD can already be measured (page 21: "CCTD becomes positive within 60 minutes...") i.e. in a phase where a myocardial infarction can possibly still be prevented by a rapid reperfusion therapy.

Therefore, it must be concluded that, contrary to the Patent Office's assertion, CCTD has an unprecedented sensitivity much better than troponin, and CCTD therefore also is highly diagnostic of unstable angina pectoris and small or minor myocardial damages (for example during "myocardial micronecrosis" and/or "ischemic membrane destruction"), much better than this is done by troponins as a marker. These results are disclosed and summarized on page 20, end of the first paragraph: "The results obtained by the applicants prove that the method is precious both with the acute myocardial infarction and also with unstable angina, in other words quite generally when there is suspicion on an acute coronary syndrome."

The advantage of CCTD over troponins, when diagnosing unstable angina pectoris with a complicated course of events, i.e., an increased risk of complications becomes obvious from the fact that "...also severe forms of unstable angina pectoris with myocytic necrosis showing elevated

troponin values in the course of events are recognized early by this method" (page 21, fourth paragraph). CCTD are capable of diagnosing mild forms of angina pectoris and additionally severe forms of angina pectoris, and with the latter forms of angina pectoris CCTD are a much better marker because the diagnosis can be made much earlier than when troponins are used. The fact that troponin may be used for a subset of indications (but not as many as CCTD) whereas CCTD is a marker for many more should not be held against CCTD as a marker for acute coronary syndromes.

In summary, the use of CCTD as a marker for early recognition and diagnosis of acute coronary syndromes, namely acute myocardial infarction and/or severe forms of unstable angina pectoris and/or patients with minor ischemic myocardial damage namely myocardial micronecroses and ischemic membrane destruction is disclosed and enabled by the present application.

Accordingly, for at least the above reasons, the foregoing rejection should be withdrawn.

Claims 1-11 stand rejected under 35 U.S.C. 112, second paragraph "as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP §2172.01." In support of the rejection, the Patent Office states the following:

> The omitted steps are: there is no correlation step set forth between the diagnosis of acute myocardial infarction and the content of choline, choline and/or trimethyl ammonium derivatives. A correlation step is necessary in the instant claims because without it one of ordinary skill would be unable to ascertain how the measurement of choline would have any relation to myocardial infarction. It is suggested that the instant claims be amended to reflect that an increased level in CCTD is the cause of the myocardial infarction diagnosis. See page 4 & page 18 of the specification.

Without acquiescing in the propriety of the rejection, Applicants have amended claims 1, 3, 4, 5, 7 and 10 to correlate an increase in the level of CCTD and/or its reaction products with the cause of the diagnosis.

According, for at least the above reasons, the foregoing rejection should be withdrawn.

Applicants note that the Patent Office has indicated that "[c]laims 1-11 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, first & second paragraph, set forth in this Office action." In view of the present amendment, it is respectfully submitted that these claims are now allowable.

In conclusion, it is respectfully submitted that the present application is now in condition for allowance. Prompt and favorable action is earnestly solicited.

If there are any fees due in connection with the filing of this paper that are not accounted for, the Examiner is authorized to charge the fees to our Deposit Account No. 11-1755. If a fee is

required for an extension of time under 37 C.F.R. 1.136 that is not accounted for already, such an extension of time is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

Kriegsman & Kriegsman

By: _____

Edward M. Kriegsman
Reg. No. 33,529
665 Franklin Street
Framingham, MA 01702
(508) 879-3500

Dated: September 22, 2003

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Fee Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on September 22, 2003

_____

Edward M. Kriegsman
Reg. No. 33,529
Dated: September 22, 2003